PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

CODE	DATE	NTD

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
101141-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002882	05.07.2004	07.07.2003

International Patent Classification (IPC) or national classification and IPC
A61K9/14, B01D9/02, A61K41/00

Applicant
ASTRAZENECA AB

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.02.2005	15.07.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002882

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-29	as originally filed
Claims, Numbers	
1-20	as originally filed
Drawings, Sheets	
1/14-14/14	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002882

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,15,16
	No:	Claims	1-5,7-14,17-20
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/GB2004/002882

Re Item V

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

D1: WO 96/32095 A (ASTRA AB ; JAKUPOVIC EDIB (SE); TROFAST JAN (SE)) 17 October 1996 (1996-10-17)

D2: WO 03/035035 A (GLAXO GROUP LTD ; MCLOUGHLIN MARTIN JOHN (GB)) 1 May 2003 (2003-05-01)

D3: WO 02/00199 A (THEOPHILUS ANDREW LEWIS ; GLAXO GROUP LTD (GB); SINGH HARDEV (GB); LAN) 3 January 2002 (2002-01-03)

D4: WO 00/38811 A (THEOPHILUS ANDREW LEWIS ; GLAXO GROUP LTD (GB); SINGH HARDEV (GB); LAN) 6 July 2000 (2000-07-06)

D5: WO 02/089942 A (BOWE MICHAEL JOSEPH ; MCCAUSLAND LINDA JANE (GB); ACCENTUS PLC (GB); S) 14 November 2002 (2002-11-14)

D6: WO 2004/034943 A (SOARE LUCICA CRISTINA ; DONNET MARCEL (CH); BOWEN PAUL (CH); ECOLE POL) 29 April 2004 (2004-04-29)

1. **Clarity**

The terms "hydrophilic" and "hydrophobic" lack clarity since there is no technical definition given as to how to decide whether a compound fulfills the one or the other criteria. It is stressed that every compound can be regarded as being hydrophilic or hydrophobic to a certain extend.

2. **Novelty**

Furthermore, the above-mentioned lack of clarity notwithstanding, the subject-matter of claims 1-5, 7-14, 17-20 is not new in the sense of Article 33(2) PCT, and therefore the criteria of Article 33(1) PCT are not met.

D1 (WO9632095) discloses a process for preparing micron-size crystalline particles of a drug substance comprising mixing a solution of a drug to a non-solvent in a container in the presence of ultrasonic energy (claim 28).

This disclosure takes away the novelty of claim 1.

Salbutamol, terbutaline, rimiterol, fenoterol, reproterol, salmeterol, formoterol,

clenbuterol iptratropium bromide, betamethsaone, fluticasone, budesonide, beclomethasone, mometasone, rofleponide, sodium cromoglycate, nedocromil sodium, salbutamol sulphate, terbutaline sulphate, fenoterol hydrobromide, salmeterol xinafoate, formoterol fumarate dihydrate, clenbuterol hydrochloride, fluticasone propionate, rofleponide palmitate, formoterol dihydrate, budesonide sulphate and terbutaline sulphate are explicitly mentioned and with particle sizes of 1μm, 1-6μm, 7μm and less than 10μm (claims 2-7 and 14-20).
Among these compounds are hydrophilic and hydrophobic compounds, **taking away the novelty of claims 2, 7, 12, 18, 19 20.**
As for the anti-solvents ethyl acetate, acetone and water are explicitly mentioned, **taking away the novelty of claims 5, 10, 11 and 13.**
As for the solvents methanol is explicitly mentioned **taking away the novelty of claims 3, 4, 8 and 9.**
A precipitation temperature of 25℃ is explicitly mentioned **taking away the novelty of claim 17.**

D2 and D3 (WO03035035 and WO0200199) disclose a process for preparing micron-size crystalline particles of a drug substance comprising mixing a solution of a drug to a non-solvent in a container in the presence of ultrasonic energy.
This disclosure takes away the novelty of claim 1.
Sodium cromoglycate, nedocromil and sodium nedocromil, beclomethasone and beclomethasone dipropionate, fluticasone and fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone, and mometasone furoate, fenoterol and fenoterol hydrobromide, formoterol and formoterol fumarate, reproterol and reproterol hydrochloride, terbutaline and terbutaline sulphate, ipratropium and ipratropium bromide and tiotropium are explicitly mentioned. **This disclosure takes away the novelty of claims 2, 7, 12, 18, 19.**
As for the anti-solvents water and ethanol are explicitly mentioned **taking away the novelty of claims 10, 11 and 13.**
As for the solvents acetone and methanol are explicitly mentioned **taking away the novelty of claims 3, 4, 8, 9.**
D3 discloses a particle size of 1-10μm **taking away novelty of claim 20.**
D3 discloses a reaction temperature of 20℃ **taking away novelty of claim 17.**

D4 (WO0038811) discloses a process for preparing micron-size crystalline particles of a drug substance comprising mixing a solution of a drug to a non-solvent in a container in the presence of ultrasonic energy.
This disclosure takes away the novelty of claim 1.
Cromoglycate, nedocromil, beclomethasone, fluticasone and fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone and mometasone furoate, triamcinolone and triamcinolone acetonide, salmeterol, fenoterol, formoterol and formoterol fumarate, reproterol, terbutaline, ipratropium and ipratropium bromide and tiotropium are explicitly mentioned. **This disclosure takes away the novelty of claims 2, 7, 12, 18, 19.**
As for the solvents acetone, water, ethanol and methanol (page 9) are explicitly mentioned **taking away novelty of claims 3, 4, 8, 9 and 13.**
As for the anti-solvents acetone, water, ethanol and methanol (page 9) are explicitly mentioned **taking away novelty of claims 5, 10 and 11.**
As for the ultrasonic frequency 20kHZ, 22 kHz and 25 kHz are explicitly disclosed **taking away novelty of claim 14.**
The disclosed particle sizes in table 2/page 16, table 4/page 19, table 6/page 21, table 7,8 and 9 **take away novelty of claim 20.**

D5 (WO02089942) discloses a process for preparing micron-size crystalline particles of a drug substance comprising mixing a solution of a drug to a non-solvent in a container in the presence of ultrasonic energy.
This disclosure takes away the novelty of claim 1.
Sodium cromoglycate is explicitly disclosed, **taking away novelty of claims 12, 18, 19.**
Hydrophilic and hydrophobic compounds which can be crystallized by the described method are disclosed (p. 21 line 6 - p. 13 line 18) **taking away novelty of claims 2 and 7.**
As for the solvents acetone and methanol are explicitly disclosed **taking way novelty of claims 3, 4, 8, 9.**
As for the anti-solvents water is disclosed, **taking away novelty of claims 10, 11 and 13.**
Reaction temperatures of 20°C are disclosed, **taking away novelty of claim 17.**
As for the ultrasonic frequency 20 kHz is explicitly disclosed, **taking away novelty of**

claim 14.

Crystal sizes of 1µm, 5µm and 10µm are explicitly disclosed, **taking away novelty of claim 20.**

3. **Inventive step**

Dependent claim 6 differs from the prior art in that the anti-solvent is acetonitrile or diethyl ether.

The choice of the anti-solvent is a matter of routine for the skilled person as this choice belongs to the nature of the compound and it's solubility in said anti-solvent (see also D9 page 6 lines 5-17; D5 page 8 lines 16-22; D3 page 9 lines 13-32; D1 page 7 lines 1-10).

No surprising/unexpected effect can be derived from a choice of an alternative which belongs to routine work.
Claim 6 therefore cannot be regarded as being inventive (Art. 33(3) PCT).

Dependent claims 15-16 differ from the prior art in that an amplitude of 12-160µm of the ultrasonic energy is defined and in that the burst rate of the ultrasonic energy is from 10% to 100% per second.

No surprising/unexpected effect can be deduced from these technical features. Thus, no inventive step can be regarded for claims 15-16 (Art. 33(3) PCT).

Re Item VI

The following documents could become relevant in some contracting states:

D6: WO 2004/034943 A (SOARE LUCICA CRISTINA ; DONNET MARCEL (CH); BOWEN PAUL (CH); ECOLE POL) 29 April 2004 (2004-04-29)